



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : C12N 15/62, C07K 19/00, 14/82, 14/52, 14/78, 14/47, 16/18, 16/28, 16/44, C12N 11, 1/19, 5/10, A61K 38/17, 39/395, G01N 33/50 // (C12N 1/21, C12R 1:19)</p>		A3	<p>(11) International Publication Number: WO 96137621</p> <p>(43) International Publication Date: 28 November 1996 (28.11.96)</p>
<p>(21) International Application Number: PCT/EP96/02230</p> <p>(22) International Filing Date: 23 May 1996 (23.05.96)</p> <p>(30) Priority Data: 95107914.4 23 May 1995 (23.05.95) EP (34) Countries for which the regional or international application was filed: DE et al.</p> <p>(71) Applicant (for all designated States except US): MORPHOSYS GESELLSCHAFT FÜR PROTEINOPTIMIERUNG MBH [DWDE]; Frankfurter Ring 193a, D-80807 Munich (DE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): PACK, Peter [DWDE]; Franz-Wolter-Strasse 4/III, D-81925 Oberfohring (DE). HOESS, Adolf [DWDE]; Wirtsbreite 21, D-83672 Warmgau (DE).</p> <p>(74) Agent: VOSSIUS AND PARTNER; P.O. Box 86 07 67, D-81634 München (DE).</p>		<p>(81) Designated States: CA, CN, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p> <p>(88) Date of publication of the international search report: 3 January 1997 (03.01.97)</p>	
<p>(54) Title: MULTIMERIC PROTEINS</p> <p>(57) Abstract</p> <p>The present invention relates to the construction and use of small multimerization devices, preferably of human origin, which self-assemble fused functional domains to multimeric and multifunctional complexes. Multimerization devices of this invention do not significantly interfere with secretion, expression yields and the independent folding of functional domains, which are attached via flexible but protease-resistant linkers. Modular gene cassettes encoding functional domains, linkers and multimerization domain can easily be combined to a cistron encoding the multimeric protein. Translation in a suitable host results in self-assembly to multimers larger than dimers. In cases, in which one or both functional domains are not expressible in sufficient yields or native fold in the same expression host, multimeric proteins can be produced, in which one or both functional domains or the multimerization device are produced separately by, e.g., in vitro translation, peptide synthesis and/or refolding and subsequently, e.g., chemically coupled to the remaining part of the multimeric protein.</p>			

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/02230

4. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	C12N15/62	C07K19/00	C07K14/82	C07K14/52	C07K14/78
	C07K14/47	C07K16/18	C07K16/44	C07K16/28	C12N1/21
	C12N1/19	C12N5/10	A61K38/17	A61K39/395	G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

3. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO,A,96 13583 (MORPHOSYS PROTEINOPTIMIERUNG ;PACK PETER (DE) ; LUPAS ANDREI (DE)) 9 May 1996 see figure 2 ---	1,25-37
X	J IMMUNOL METHODS, JAN 27 1995, 178 (2) P201-9, NETHERLANDS, XP000608189 DUBEL S ET AL: "Bifunctional and multimeric complexes of streptavidin fused to single chain antibodies (scFv)." see the whole document ---	1,25-41

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Date of the actual completion of the international search

5 November 1996

Date of mailing of the international search report

15.11.96

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/02230

A. CLASSIFICATION OF SUBJECT MATTER
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>HUM ANTIBODIES HYBRIDOMAS, 1995, 6 (3) P93-101, UNITED STATES, XP000607119 KIPRIYANOV SM ET AL: "Single-chain antibody streptavidin fusions: tetrameric bifunctional scFv-complexes with biotin binding activity and enhanced affinity to antigen." see figure 5 ---</p> <p>WO,A,93 15210 (MERCK PATENT GMBH) 5 August 1993 cited in the application see page 10 - page 13; examples 1-4 ---</p> <p>---</p>	<p>1,25-41</p> <p>1-3, 12-16, 25-41</p> <p>-/-</p>

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/02230

(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J MOL BIOL, FEB 10 1995, 246 (1) P28-34, ENGLAND, XP000607470 PACK P ET AL: "Tetraivalent miniantibodies with high avidity assembling in Escherichia coli." see the whole document ---	1-7, 12-16, 25-41
Y	FEBS LETTERS, vol. 341, 1994, AMSTERDAM NL, pages 54-58, XP002017642 EFIMOV VP ET AL: "The thrombospondin-like chains of cartilage oligomeric matrix protein are assembled by a five-stranded alpha-helical bundle between residues 20 and 83" cited in the application see the whole document ---	1-7, 12-16, 25-41
Y	BIOCHEMISTRY, vol. 33, 1994, EASTON, PA US, pages 8361-8366, XP002017643 LAI CK ET AK: "Crystal structure of recombinant human platelet factor 4" cited in the application see page 4 ---	1-7, 12-16, 25-41
Y	PROC NATL ACAD SCI U S A, SEP 13 1994, 91 (19) P8974-8, UNITED STATES, XP000608191 SAKAMOTO H ET AL: "Specific sequences from the carboxyl terminus of human p53 gene product form anti-parallel tetramers in solution." cited in the application see abstract ---	1-3, 12-16, 25-41
Y	SCIENCE, MAR 10 1995, 267 (5203) P1498-502, UNITED STATES, XP000608194 JEFFREY PD ET AL: "Crystal structure of the tetramerization domain of the p53 tumor suppressor at 1.7 angstroms." cited in the application see abstract -----	1-3, 12-16, 25-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/02230

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9613583	09-05-96	NONE	
WO-A-9315210	05-08-93	AU-A- 3410093 CA-A- 2128511 CZ-A- 9401757 EP-A- 0654085 HU-A- 68798 JP-T- 7503366 NO-A- 942750	01-09-93 05-08-93 15-12-94 24-05-95 28-07-95 13-04-95 13-09-94